UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,734	04/24/2008	Peter Kufer	028622-0155	2784

22428 7590 02/01/2011
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
DUFFY, BRADLEY	
ART UNIT	PAPER NUMBER
1643	
MAIL DATE	DELIVERY MODE
02/01/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,734	KUFER ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/10/2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 4, 6-26 and 27-31* is/are pending in the application.

4a) Of the above claim(s) *11-12, 16-22 and 27-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 6-10, 13-15, 23-25 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *8/82006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/8/06,3/31/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed November 10, 2010, acknowledged and has been entered.

Claims 1, 11, 12, 13, 14, 17 and 27 have been amended. Claims 2, 3, 5 and 26 have been canceled.

2. The election with traverse filed November 10, 2010, is acknowledged and has been entered.

Applicant has elected to prosecute the invention of the Group I, drawn to bispecific binding molecules, whereby said molecule comprises at least two domains, (a) wherein one of said at least two domains specifically binds to/interacts with the human CD3 complex, wherein said domain comprises an amino acid sequence of an antibody derived light chain, wherein said amino acid sequence is (i) an amino acid sequence of SEQ ID NO: 2; (ii) an amino acid sequence encoded by a nucleic acid sequence corresponding to SEQ ID NO: 1; (iii) an amino acid sequence encoded by a nucleotide sequence hybridizing with the complementary strand of a nucleic acid sequence as defined in (ii) under stringent conditions; and (iv) an amino acid sequence encoded by a nucleic acid sequence which is degenerate as a result of the genetic code to a nucleotide sequence of any one of (ii) and (iii) with the proviso that amino acid sequences according to (i) to (iv) comprise amino acid substitutions in the CDR regions of the light chain in positions L24, L54 and L96 according to the Kabat system; and (b) wherein a second domain is or contains at least one further antigen-interaction-site and/or at least one further effector domain.

Applicant has further elected the species of the domain that binds the human CD3 complex comprising of the amino acid sequence of SEQ ID NO: 10 or is encoded by the nucleic acid sequence of SEQ ID NO: 9 and the species of second domain specifically binding/interacting with EpCAM.

Finally, while it is noted that Applicant did not identify the claims that read

on the species as required, rather than mailing a notice of non-responsive amendment, it was determined that the specification sets forth that:

> "It is particularly envisaged that the bispecific binding molecule of the invention which specifically binds to/interacts with the CD3 and the EpCAM molecule is characterized in that said second domain comprises or consists of an amino acid sequence selected from the group of: (a) an amino acid sequence corresponding to SEQ ID NO.: 22, 24, 26, 28, 30 or 32; (b) an amino acid sequence encoded by a nucleic acid sequence corresponding to SEQ ID NO.: 21, 23, 25, 27, 29 or 31; (c) an amino acid sequence encoded by a nucleic acid sequence hybridizing with the complementary strand of a nucleic acid sequence as defined in (b) under stringent hybridization conditions; and (d) an amino acid sequence encoded by a nucleic acid sequence which is degenerate as a result of the genetic code to a nucleotide sequence of any one of (b) and (c)"

(see page 16) and that SEQ ID NO.: 34 and 36 give the amino acid sequences of bispecific molecules that bind CD3 and EpCAM (see page 34). Furthermore, based on the sequence search the amino acid sequence of SEQ ID NO:10 is comprised within the amino acid sequence of SEQ ID NO: 14. Accordingly, claims 1, 4, 6-10, 13-15, 23-25 and 31 read on the elected invention and species of invention.

3. Claims 1, 4, 6-25 and 27-31 are pending in the application.

4. Claims 11-12, 16-22 and 27-30 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention or non-elected species of invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 10, 2010.

5. Claims 1, 4, 6-10, 13-15, 23-25 and 31 are under examination.

Election/Restrictions

6. Applicant's traversal of the restriction and election requirement set forth in the previous office actions is acknowledged.

Applicant's arguments have been carefully considered but have not been found persuasive for the following reasons:

In the response filed November 10, 2010, Applicant has argued that the requirement is moot because the independent claim is amended to "an antibody derived light chain having the amino acid sequence of SEQ ID NO.: 10 or its nucleic acid sequence of SEQ ID NO.:9".

In response, independent claim 1 recites an amino acid sequence of an antibody derived light chain **encoded** by a nucleic acid sequence of SEQ ID NO:9, so the amendment has not rendered the requirement moot as Group I is drawn to bispecific binding molecules comprised of amino acids, while Group II is drawn to nucleic acid sequences.

Secondly, Applicant has argued that the Office has misapplied the unity of invention standard and the current claims comply with this international standard because the International Bureau for the PCT application did not find a unity of invention issue, searched all of the claims and was able to make a determination regarding the patentability of the subject matter of all claims in this application and that the search of Group II along with Group I and all species are not unduly burdensome.

In response, the Examiner is not bound by the actions that occurred in the international phase, as MPEP 1893.03(d) clearly states, "If the examiner finds that a national stage application lacks unity of invention under § 1.475, the examiner may in an Office action require the applicant in the response to that action to elect the invention to which the claims shall be restricted." National Stage applications must be examined for unity of invention consistent with the Patent Cooperation Treaty and it is noted in the restriction requirement mailed September 13, 2010, the Examiner determined that claim 1 lacks an inventive step over the prior art. Therefore, the Examiner determined in examining the inventions for unity of invention consistent with the Patent Cooperation Treaty that the inventions are not so linked as to form a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features.

Secondly, in response to Applicant's argument that there would not be a

search burden to consider the inventions of Group I and Group II and all species, the Examiner notes that unity of invention restriction practice for national stage applications does not require that there be a serious search burden (see MPEP 1893.03(d)).

Finally, Applicant has provided no evidence to establish why the remaining groups share unity of invention as required under PCT Rule 13 or why the requirement for restriction is improper.

Therefore, for these reasons and the reasons set forth in the Office action mailed September 13, 2010, these inventions do not share unity of invention as required under PCT Rule 13 and the restriction/election requirement is deemed proper and therefore made FINAL.

Information Disclosure Statement

7. The references cited in the information disclosure statements filed on 8/8/06 and 3/31/09, have been considered.

Priority

8. Applicant's claim under 35 USC §§ 119 and/or 120 for benefit of the earlier filing date of EP 04003445.6 filed February 16, 2004

However, claims 1, 4, 6-10, 13-15, 23-25 and 31 do not properly benefit under 35 U.S.C. §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112.

See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of the claims is deemed the filing date of PCT/EP05/001573, namely February 16, 2005.

Specification

9. The disclosure is objected to because of the following informalities:

a. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is SEPHADEX® (see, e.g., page 32).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ®, ™), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

b. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

Examples of such impermissible disclosures appear in the specification at, e.g., page 12 and 31.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-

executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference. See 37 CFR § 1.57.

MPEP 608.01(p) does not provide for incorporation of essential *or* non-essential material by reference to, for example, hyperlinks or other forms of browser-executable code, so as to incorporate the contents of websites so designated or identified. Essential subject matter may only be incorporated by reference to (1) US patents and pending US applications, or patents or other publications published by a foreign country or a regional patent office, (2) non-patent publications, (3) a US patent or application which itself incorporates material by reference, or (4) a foreign application. Non-essential information may be incorporated by reference to (1) patents or applications published by the United States, or patents or other publications published by a foreign country or a regional patent office, (2) prior filed, commonly owned US applications, (3) non-patent publications. Not provided for by MPEP 608.01(p) is the incorporation of any material, essential or not, by reference to Internet address identifying a site, e.g., on the World Wide Web.

Appropriate correction is required.

c. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Objections

10. Claims 23-25 and 31 are objected to as being drawn in the alternative to the subject matter of non-elected inventions (e.g., the invention of Group II).

11. Claims 1, 4, 6-10, 13-15, 23-25 and 31 are objected to for reciting “one further" in claims 1, 7 and 15 or "a further" in claim 9.

In this case the objection could be obviated by amending the claims to remove the word “further"

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1, 4, 6-10, 13-15, 23-25 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1, 4, 6-10, 13-15, 23-25 and 31 are indefinite in the recitation of "interacts with" or “antigen-interaction site” in the claims. This recitation renders the claims indefinite because the claims also recite that the domain specifically binds, so it is apparent that the metes and bounds of the phrase "interacts with” or “antigen-interaction site” is different that specific binding, but it is unclear how interacting is different that binding. If antigen interaction is different than antigen binding what is the interaction? For example, must the domain interact with the antigen by being conjugated to it, must it interact by being in the same solution as the antigen, must it interact by being a catalytic domain that cleaves the antigen or does the domain interact with the antigen in some other way? Without knowing how the domain interacts with the antigen the claims cannot be unambiguously construed.

Amending the claims to remove e.g., “interacts with” and to recite “antigen-binding domain" would obviate this rejection.

(b) Claims 1, 4, 6-10, 13-15, 23-25 and 31 are indefinite in the recitation of "or is encoded” in the claims. This recitation renders the claims indefinite because it is unclear what is encoded by a nucleic acid sequence of SEQ ID NO:9. For example, the claims recite a bispecific molecule, a domain, and an antibody derived light chain and it is unclear what the sequence encodes.

Amending the claims to specify what the sequence encodes would obviate this rejection.

(c) Claims 1, 4, 6-10, 13-15, 23-25 and 31 are indefinite in the recitation in claim 1 of "wherein one of said at least two **domains** specifically binds to/interacts with the human CD3 complex, **wherein said domain**." In this case, because the molecule recites two domains, reference to said domain lacks proper antecedent basis and it is unclear which domain is being referred to. Thus, the claims fail to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

This rejection could be obviated by amending the claim to recite e.g., "wherein the domain that specifically binds the human CD3 complex comprises…".

(d) Claims 13 and 14 are also indefinite in the recitations of "an amino acid sequence corresponding to" and "encoded by a nucleic acid sequence corresponding to" because it cannot be determined to what extent an amino acid sequence or a nucleic acid sequence must *correspond to* the recited sequences. For example, must the amino acid sequence correspond 100% to the recited sequence, correspond to some lesser extent, only correspond by being a sequence of a domain that binds the same antigen, or can the amino acid sequence *correspond* in some other way? Thus, it is submitted that the claims fail to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

(e) Claim 25 is also indefinite in the recitation of a composition that further comprises methods for detection. Since compositions are products they cannot comprise methods *per se* and it cannot be determined what is

contemplated by a composition further comprising methods for detection. Thus, it is submitted that the claims fail to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

Therefore, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1, 4, 6-10, 13-15, 23-25 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a “written description” rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter “Guidelines”). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, “the issue of a lack of written description may arise even for an original claim when an aspect of the claimed

invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

Furthermore, the Federal Circuit has commented that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)). See *Noelle v. Lederman*, 69 USPQ2d 1508 (CAFC 2004).

Finally, with further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

(a) In this case, the claims are drawn to a structurally and functionally diverse genus of bispecific binding molecules comprising at least two domains, wherein one “domain interacts with human CD3” and a second domain that contains an “antigen- interaction-site and/or at least one further effector domain” and as drawn to the elected species of invention, wherein the second domain interacts with EpCAM.

Notably, as set forth at page 10, the specification indicates that "[a]ccording to the present invention "bispecific binding molecules" are (poly)peptides which necessarily specifically bind with one domain to the human CD3 complex and/or its individual components”. Furthermore, while the specification discloses various bispecific antibodies, wherein the bispecific antibody comprises one antigen-binding domain comprising a variable light chain domain and a variable heavy chain domain that specifically binds a first antigen, such as the human CD3 complex and wherein the bispecific antibody comprises another antigen-binding domain comprising a variable light chain domain and a variable heavy chain domain that specifically binds a second antigen, such as EpCAM (see e.g., Examples 2-6 pages 34-39), the specification does not identify any bispecific molecule that *interacts* with an antigen in any other way.

For example, other than the antigen-binding domain comprising a variable light chain domain and a variable heavy chain domain that specifically *binds* an antigen, the specification does not identify any structure that interacts with an antigen, so it is submitted that one of skill in the art would not find the disclosed antigen-binding domains representative of a genus of antigen-interaction sites because, as will be explained in more detail in the written description rejection below, the structural basis of antigen-antibody recognition is reviewed in Mariuzza et al. (Annu. Rev. Biophys. Biophys. Chem. 1987; 16: 139-159) which teaches that naturally occurring antibodies that specifically bind antigens comprise two polypeptides, the so-called light and heavy chains, which fully comprises six “complementarity-determining regions” (CDRs), three each from

the light and heavy chains, and the claimed interaction sites need not be an antigen-binding domain comprising a variable light chain domain and a variable heavy chain domain that specifically binds a antigen.

Furthermore, it is noted that the second domain need not even bind or interact with any antigen, as the second domain may be an “effector domain" and the specification also fails to adequately describe the claimed *bispecific* binding molecules, because one of skill in the art could not immediately envision, recognize or predict which effector domains also have the function of interacting with an antigen in a *bispecific* binding molecule.

Given the lack of particularity with which the genus of **bispecific** binding molecules comprising at least two domains, wherein one “domain interacts with human CD3” and a second domain that contains an “antigen-interaction-site and/or at least one further effector domain”, to which the claims are directed, are described in the specification, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of the claimed genus, to which the claims are directed; and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

(b) Secondly, the claims also encompass a structurally and functionally diverse genus of domains that need only comprise or consist of **an amino acid** sequence of an antibody ***derived*** light chain having the amino acid sequence of SEQ ID NO.: 10 or is encoded by **a nucleic acid** sequence of SEQ ID NO.: 9, according to claim 1 and according to claims 13 and 14 the second domain need only comprise or consist of **an amino acid** sequence corresponding to SEQ ID NO.: 22, 24, 26, 28, 30, 32, 34, or 36 or an amino acid sequence encoded by **a nucleic acid sequence** corresponding to SEQ ID NO.: 21, 23, 25, 27, 29, 31, 33 and 35. Notably, while these claims are written with comprising, i.e., open language, the term "comprising" encompasses the term "consisting of", so the claims reasonably include domain consisting of only **an amino acid** sequence of

an antibody ***derived*** light chain. Furthermore, because the claims recite "**an** amino acid sequence" or "**a** nucleic acid sequence", as opposed to "**the** amino acid sequence" or "**the** nucleic acid sequence", the claims are broadly but reasonably being interpreted as directed to a genus of structurally and functionally diverse domains that need only comprise a domain that comprises or consists of **an** amino acid sequence of an antibody ***derived*** light chain having the amino acid sequence of SEQ ID NO.: 10 or **an** amino acid sequence that is encoded by **a nucleic acid** sequence of SEQ ID NO.: 9 and the second domains are broadly but reasonably being interpreted as directed to a genus of structurally and functionally diverse domain that need only to comprise of consist of **an amino acid** sequence that **corresponds to** the recited sequences in some undefined way. Notably, one of skill in the art readily appreciates that because amino acid sequences provide merely descriptive information about a protein, that an amino acid sequence of SEQ ID NO:9 would include any 2, 3, 4, 5, 6, etc., consecutive amino acids set out in SEQ ID NO:9 because each 2, 3, 4, 5, 6, etc., consecutive amino acids set out in SEQ ID NO:9 is an amino acid sequence. Accordingly, because the domains encompassed by this genus could have virtually any structure, it is apparent that such domains do not share any particularly identifying (i.e., substantial) structural feature which would allow one if skill in the art to immediately envision, recognize or distinguish which domains comprising an amino acid sequence of SEQ ID NO:9 or an amino acid sequence encoded by a nucleic acid sequence of SEQ ID NO:10 would specifically bind the human CD3 complex. Similarly, because second domains that *correspond to* the recited sequences could have any structure, it is apparent that such domains do not share any particularly identifying (i.e., substantial) structural feature which would allow one if skill in the art to immediately envision, recognize or distinguish the domains from any other. Notably, the second domains need not have any particular structure or function and therefore, there can be no correlation of any particular identifying structural feature with any function of the recited domain.

In this case, it is well-established in the art that there is a high degree of

unpredictability in determining the three-dimensional structure and function of a given protein *a priori* given its amino acid sequence.

As evidenced by Jones (Pharmacogenomics Journal, 1:126-134, 2001), protein structure "prediction models are still not capable of producing accurate models in the vast majority of cases" (page 133, 3rd paragraph). Furthermore, Tosatto et al state, "the link between structure and function is still an open question and a matter of debate" (Current Pharmaceutical Design, 12:2067-2086, 2006, page 2075, 1st new paragraph). Therefore, even if the skilled artisan were able to submit a complete list of all the possible immunoglobulins which fall within the scope of the claims, the skilled artisan would not be able to immediately envision, recognize or predict the three-dimensional structure and function of a given immunoglobulin *a priori* based on its amino acid sequence.

Furthermore, because of the open language of claim 1 and further supported by the specification at page 13, first paragraph, the first domain can consist of the amino acid sequence of SEQ ID NO: 10 (light chain of the humanized CD3 binding molecule of the invention), and the second domain can consist of any amino acid sequence corresponding to SEQ ID NO.: 22, 24, 26, 28, 30 or 32 (each of these sequences only define a light chain variable domain of an antibody **or** a heavy chain variable domain of an antibody) as set forth in the specification at page 16.

In this case, the specification also fails to adequately describe the domains because one of skill in the art could not immediately envision, recognize or predict whether a domain consisting of only a light chain, only a heavy chain or only part of a claimed sequence would be a domain that has the required binding function.

To elaborate on why the claimed domains consisting of only a light chain or only a heavy chain and fragments thereof lack adequate written description, Mariuzza et al. (Annu. Rev. Biophys. Biophys. Chem. 1987; 16: 139-159) reviews the structural basis of antigen-antibody recognition and teaches that a naturally occurring antibody comprises two polypeptides, the so-called light and heavy

chains. The antigen-combining site of an antibody is a three-dimensional structure, which fully comprises six “complementarity-determining regions” (CDRs), three each from the light and heavy chains. The amino acid sequences of the CDRs are hypervariable, as the amino acid residues contained within the CDRs determine much of antibody's antigen-binding specificity. Of the amino acid residues of the antibody contacting the antigen, six are within the light chain, nine are within the heavy chain, and two are within the constant or nearly constant “framework” regions.

In view of Mariuzza et al., it is apparent that domains having less than all six CDRs that form the antigen binding site of an antibody in their proper context of heavy and light chain variable domains does not suffice to describe the particularly identifying structural feature of the domain that correlates with the domains ability to bind to the antigen. Absent a description of the at least minimal structural features correlating with a functional ability to bind to a particular antigen, which are shared by members of a genus commonly sharing this function, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish members of the genus from other domains. For this reason, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Notably, in this case, while the specification discloses various bispecific antibodies, wherein the bispecific antibody comprises one antigen-binding domain comprising **both** a variable light chain domain and a variable heavy chain domain and this domain specifically binds the human CD3 complex and wherein the bispecific antibody comprises another antigen-binding domain comprising **both** a variable light chain domain and a variable heavy chain domain and this domain specifically binds a second antigen, such as EpCAM (see e.g., Examples 2-6 pages 34-39), the specification does not identify any bispecific molecule comprising just a light chain variable domain or fragment thereof that that binds to the human CD3 complex and does not disclose any light chain variable

domain that by itself binds to EpCAM, any heavy chain variable domain that by itself binds to EpCAM or any fragments thereof that by themselves bind to EpCAM.

In this case, because the antigen-binding domains which are disclosed as binding the human CD3 complex and EpCAM are from antibodies comprising a light and heavy chain and because the specification does not present any evidence that just a light chain, just a heavy chain or any fragment thereof of these domain has the ability to bind to the human CD3 complex or EpCAM, it is submitted that one of skill in the art would not immediately envision or recognize that e.g., domains consisting of just a light chain would have the affinity and specificity of the parent antibody.

The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See Noelle v. Lederman, 69 USPQ2d 1508 1514 (CA FC 2004) (citing Enzo Biochem II, 323 F.3d at 965; Regents, 119 F.3d at 1568).

Additionally, "generalized language may not suffice if it does not convey the detailed identity of an invention." University of Rochester v. G.D. Searle Co., 69 USPQ2d 1886 1892 (CAFC 2004).

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (CAFC 1991); University of Rochester v. G.D. Searle Co., 69 USPQ2d 1886 1892 (CAFC 2004).

"Guidelines" states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the

invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104). Moreover, because the claims are directed to a genus of structurally disparate domains and fragments thereof, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

Once again, the specification only presents evidence that bispecific molecules comprising antigen-binding domains comprising all 6 CDRs of two respective parent antibodies in the proper context of heavy and light chain frameworks as having the function of binding the human CD3 complex and EpCAM. Accordingly, one of skill in the art would not be able to immediately envision, recognize or predict the structure of bispecific molecules composing less than all 6 of the recited CDRs in the proper context of heavy and light chain frameworks of both parent antibodies which would have the function of bniding the human CD3 complex and EpCAM and would not recognize that Applicant was in possession of the claimed invention.

Given the lack of particularity with which the bispecific molecules to which the claims are directed, are described in the specification, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of the claimed genus, to which the claims are directed; and

therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

(c) In this case, 8 is further drawn to a second domain that that specifically recognizes a structurally and functionally diverse genus of “tumor specific molecules”, and it is submitted that one of skill in the art could not immediately envision, recognize or predict if any given antigen is a “tumor specific molecule” because many antigens that expressed by tumors have not been structurally and functionally characterized in all tumors and healthy tissues such that their expression only in tumors cannot be immediately envisioned, recognized or predicted. Notably, at page 14 the specification only characterizes one cell surface antigen which as tumor specific and that is EGFRV-III, but Okomaoto et al (Cancer Sci., 94(1):50-56, 2003) teach that rather than being tumor specific, EGFRV-III is also expressed in some healthy lung tissue (see entire document, e.g., Figure 1).

Accordingly, it is apparent that one of skill in the art could not immediately envision, recognize or predict whether any given antigen was "tumor specific" or not and therefore could not distinguish at least most of its members from other antigens.

Given the lack of particularity with which the “tumor specific molecules”, to which the claims are directed, are described in the specification, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of the claimed genera, to which the claims are directed; and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

16. Claims 1, 4, 6-10, 13-15, 23-25 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and**

using a bispecific binding molecule, whereby said molecule comprises at least two domains, (a) wherein one of said at least two domains specifically binds human CD3 complex, wherein the domain that specifically binds human CD3 complex comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 10 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 12 and (b) wherein the second domain comprises an antigen binding-domain that specifically binds a cell surface molecule, wherein the antigen binding-domain that specifically binds a cell surface molecule comprises a light chain variable domain and a heavy chain variable domain and, as drawn to the elected species of invention, **while being enabling for making and using** bispecific binding molecules, whereby said molecule comprises at least two domains, (a) wherein one of said at least two domains specifically binds human CD3 complex, wherein the domain that specifically binds human CD3 complex comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 10 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 12 and (b) wherein the second domain comprises an antigen binding-domain that specifically binds EpCAM, wherein the antigen binding-domain that specifically binds EpCAM comprises a light chain variable domain and a heavy chain variable domain and, as drawn to the elected species of invention, **while being enabling for making and using** bispecific binding molecules, whereby said molecule comprises at least two domains, (a) wherein one of said at least two domains specifically binds human CD3 complex, wherein the domain that specifically binds human CD3 complex comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 10 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 12 and (b) wherein the second domain comprises an antigen binding-domain that specifically binds EpCAM, wherein the antigen binding-domain that specifically binds EpCAM comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO:24 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:22 **or** (b) wherein the second domain

comprises an antigen binding-domain that specifically binds EpCAM, wherein the antigen binding-domain that specifically binds EpCAM comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO:28 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:26 **or** (b) wherein the second domain comprises an antigen binding-domain that specifically binds EpCAM, wherein the antigen binding-domain that specifically binds EpCAM comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO:32 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:30 and **while being enabling for making and using** any bispecific molecules encompassed by the claims, which have been described by the prior art, **does not reasonably provide enablement for making and using** the full scope of the claimed bispecific molecules such as bispecific molecules comprising domains that only consist of a light chain, consist only of a heavy chain or consist only of a fragment of a light chain or a heavy chain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of Mineral Separation v. Hyde, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue”. These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior

art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

In this case, the claims have been described supra in the above written description rejection.

As a first point, since the claims are not limited to bispecific molecules that that specifically bind to well-characterized antigens, but to a genus of "bispecific molecules" that need only interact with human CD3 complex or contain an interaction site, it is submitted that one of skill in the art would be subject to undue experimentation to use such interacting molecules as the specification only provides specific, non-general guidance as to how to use bispecific molecules that **bind** to two different antigens.

Furthermore, with respect to bispecific molecules that bind to the human CD3 complex and EpCAM which need not comprise both a light and heavy chain variable domain comprising all 6 CDRs in the proper context of heavy and light chain frameworks of two respective parental antibodies, one of skill in the are would be subject to undue and unreasonable experimentation to make bispecific molecules commensurate with the full scope of the claimed invention. In this case, the specification, for example, does not provide any specific, non-general guidance as to how to make a bispecific molecule that binds to the human CD3 complex comprising a first domain that consists of a light chain variable domain that consists of the amino acid sequence of SEQ ID NO:10, so it is submitted that only of skill in the art would be subject to undue experimentation to make such a molecule.

As noted by Mariuzza et al. (*supra*), it is well established fact in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable domains of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol. 79: page 1979-1983). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antigen-binding domains that do not contain all of the 6 CDRs of the parent antibody in their proper context of heavy and light chain variable domains, respectively, would retain the epitope-binding function of the parent antibody.

Thus, while the prior art teaches some understanding of the structural basis of antigen-antibody recognition, it is aptly noted that the art is characterized by a high level of unpredictability, since the skilled artisan still cannot accurately and reliably predict the consequences of amino acid substitutions, insertions, and deletions in the antigen-binding domains and surrounding framework regions of antibodies.

The art of engineering functional recombinant binding domains, such as those to which the claims are directed, is even more confounded by findings that residues, which are positioned outside the recognized boundaries of the

canonical CDRs, may contribute substantially to the interaction of an antibody and an antigen. For example, MacCallum et al. (*J. Mol. Biol.* 1996 Oct 11; **262** (5): 732-745) describes the discovery that although the residues of CDR3 of the heavy and light chains are dominant determinants of the interaction, a number of essential residues contacting the antigen have been placed outside the regions that are recognized using the conventional or standard definitions of the CDRs, which are generally used to define the components of the antigen binding site of the antibody; see entire document (e.g., page 733, column 2). Moreover, MacCallum et al. teaches an appreciation of the fact that residues within the CDRs that do not actually make contact with the antigen may be important because of their contributions to the conformation of the antibody's antigen recognition site; see, e.g., page 735, column 1.

Making further apparent the unpredictability of the importance of residues within the CDRs and other parts of an antibody, which must instead be determined empirically, Holm et al. (*Mol. Immunol.* 2007 Feb; **44** (6): 1075-1084) describes the mapping of residues important to the interaction of an anti-cytokeratin antibody with the antigen, where although residues in the CDR3 of the heavy chain were determined to be essential, they disclose their *unexpected* finding that a residue in CDR2 of the light chain forms a necessary part of the antigen binding site of the antibody contacting the antigen; see entire document (e.g., the abstract). Thus, as recently as 2007, there are reports indicating despite the progress made toward understanding the interactions of antibodies and antigens, because of the unpredictable nature of the art, much information concerning the specificity and/or affinity of any given antibody cannot be gleaned by routine and conventional experimentation, but instead must be gathered by rigorous and undue experimentation. For these reasons, one of skill in the art would be subject to undue and unreasonable experimentation to make bispecifc molecules commensurate in scope with the claimed bispecifc molecules.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

In conclusion, upon careful and full consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

18. Claims 1, 7-8, 13-15, 23, 24 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/47531 A2, (Smith et al, 1998).

The claims are herein drawn to a bispecific binding molecule, whereby said molecule comprises at least two domains, (a) wherein one of said at least two domains specifically binds to the human CD3 complex, wherein the domain that specifically binds to the human CD3 complex comprises **an** amino acid sequence, which is broadly, but reasonably interpreted as at least two consecutive amino acids of an antibody derived light chain having the amino acid sequence of SEQ ID NO: 10 and a second domain that binds a cell surface molecule. Notably, as it is unclear how the amino acid sequence of the second domain of claims 13 and 14 must correspond to the recited sequences, the claims are broadly, but reasonably drawn to any second domain as all second domains may be said to correspond to some extent or in some way with the recited sequences. Dependent claims further recite that the second domain is humanized and compositions comprising said bispecific binding molecule and suitable carriers and kits comprising said bispecific binding molecule. Furthermore, claim 8 has been included in this rejection and the below rejections because although Smith et al do not characterize their cell surface molecule as "tumor specific" as detailed in the above written description rejection a "tumor specific" antigen is indistinguishable from any other cell surface antigen. Finally, claim 25 has not been included in this or any of the below rejections as it cannot be determined how a composition comprises methods as detailed in the above 35 USC 112, second paragraph rejection.

Smith et al teach bispecific anti-CD3-Fos x anti-CD4-Jun binding molecules wherein the antigen binding domain that binds the human CD3 complex is from an antibody designated OKT3 which comprises two consecutive amino acids of an antibody derived light chain having the amino acid sequence of SEQ ID NO: 10 a light chain and CD4 is a cell surface molecule (see entire document, e.g, abstract, SEQ ID NO:6, Figures 1 and 2, page 61). Smith et al further teach that that antigen-binding domains may be humanized, compositions comprising said bispecific binding molecule and suitable carriers (see e.g., pages 50 and 56), which while not characterized as a "kit" *per se* would be inherently

provided in a kit form for sale. It is also noted that the claimed "kit" is not further characterized as comprising anything other than the bispecific binding molecule so the compositions of Smith et al are materially and structurally indistinguishable from the claimed kits.

Accordingly, absent a showing of any difference, the bispecific binding molecules of Smith et al are materially and structurally indistinguishable from the claimed bispecific binding molecules and Smith et al anticipate the claimed invention.

19. Claims 1, 4, 7-10, 13-14, 23, 24 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Mack et al (J. Imm., 158:3965-3970, 1997).

Claims 1, 7-8, 13-14, 23, 24 and 31 are described supra. Dependent claims 4, 9 and 10 are further drawn to the domains of the bispecific molecule being scFvs and wherein the second domain specifically binds EpCAM.

Mack et al teach a bispecific binding molecule comprising an antigen binding domain that is an scFv that binds the human CD3 complex and that comprises an antigen binding domain that is an scFv that binds EpCAM (see entire document, e.g, abstract, page 3966). Mack et al further teach that antigen-binding domains may be humanized and compositions comprising said bispecific binding molecule in aqueous solutions that inherently comprise suitable carriers, such as water (see e.g., page 3967). Furthermore, the claimed "kit" is not characterized as comprising anything other than the bispecific binding molecule so the compositions of Mack et al are materially and structurally indistinguishable from the claimed kits.

Finally, while Mack et al does not provide the amino acid sequence of the domain that binds human CD3 complex, it is noted that the amino acid sequence of the bispecific binding molecule of Mack et al is an inherent property and the Office lacks the resources and facilities to determine the sequence of the bispecific binding molecule of Mack et al. Notably, as SEQ ID NO: 10 comprises 105 amino acid sequences that are two amino acids in length it is submitted that

the domain of Mack inherently comprises a two amino acid sequence shared with an amino acid sequence of SEQ ID NO:10. Consequently, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed domain comprising an amino acid sequence of SEQ ID NO:10 is different than the domain of Mack et al.

Accordingly, Mack et al teach products that are materially and structurally indistinguishable from the instantly claimed products. Therefore, absent a showing of any difference, the products disclosed by the prior art are deemed to anticipate the claimed invention.

20. Claims 1, 4, 7-10, 13-15, 23, 24 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Kufer et al (US 20070081993 A1, effective filing date 05/26/2004).

The claims are described supra.

Kufer et al teach bispecific single chain anti-CD3 x anti-EpCAM binding molecules wherein the antigen binding domain that binds the human CD3 complex comprises two consecutive amino acids of an antibody derived light chain having the amino acid sequence of SEQ ID NO: 10 a light chain (see entire document, e.g, abstract, pages 4 and 8 and Figure 3). Kufer et al further teach that the antigen-binding domains may be humanized, compositions comprising said bispecific binding molecule and suitable carriers and the bispecific molecules comprised in a "kit" (see e.g., pages 5, 11 and 12).

Accordingly, absent a showing of any difference, the bispecific binding molecules of Kufer et al are materially and structurally indistinguishable from the claimed bispecific binding molecules and Kufer et al anticipate the claimed invention.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

22. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 1 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mack et al (J. Imm., 158:3965-3970, 1997), in view of Queen et al (U.S. Patent 5,530,101, 1996).

Claims 1 and 15 described supra.

Mack et al that which is set forth in the above 102(b) rejection. While

Mack et al teach a bispecific binding molecule structurally and materially indistinguishable from the claimed bispecific binding molecule, Mack et al do not expressly teach humanizing the antigen-binding domains. This deficiency is made up for in the teachings of Queen et al.

Queen et al teach methods of humanizing murine monoclonal antibodies for human therapy and that such antibodies have advantages in being less immunogenic in humans (see entire document, e.g., columns 1 and 19-20).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to humanize the antigen-binding domains of Mack et al in view of Queen et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention to humanize the domains as Queen teach methods of humanizing murine monoclonal antibodies and that such antibodies have advantages over the murine antibody. Furthermore, since Mack et al teach that their bispecific molecule displays tumor cell cytotoxicity, one of skill in the art would have been further motivated to humanize it to reduce immunogenicity of the construct in humans. Thus, there would be an advantage and a reasonable expectation of success in humanizing the bispecific molecule of Mack et al in view of Queen et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

24. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed.

Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

25. Claims 1, 4, 7-10, 13-15, 23, 24 and 31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12, 25 and 26 of copending Application No. 10/554,851. Note: the claims of Application No. 10/554,851 are now allowed, once the application issues as a patent the rejection will no longer be provisional. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

The instant claims have been described supra.

Claims 12, 25 and 26 of copending Application No. 10/554,851 are drawn to single chain bispecific binding molecules that bind human CD3 and EpCAM comprising the amino acid sequence of SEQ ID NO:44 which shares two consecutive amino acids with the instantly recited SEQ ID NO:10 and compositions or kits comprising said bispecific binding molecules.

While the claims do not further set forth that the antigen-binding domains may be humanized, it is noted that the specification of '851 discloses that the antigen-binding domains may be humanized (see e.g., page 14)

Notably, MPEP § 804.II.B.1 states that when considering obviousness-type double patenting issues, the disclosure of the patent [or copending application] cannot be used as prior art, but "[t]his does not mean one is precluded from all use of the patent disclosure". MPEP § 804.II.B.1 continues,

"[t]he specification can always be used as a dictionary to learn the meaning of a term in the patent [or application] claim". Citing *In re Vogel and Vogel*, 164 USPQ 619 (CCPA 1970), MPEP § 804.II.B.1 states, "one must first 'determine how much of the patent [or application] disclosure pertains to the invention claimed in the patent [or application]' because only '[t]his portion of the specification supports the patent claims and may be considered' " and " 'this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, **since only the disclosure of the invention claimed in the patent may be examined**" [emphasis added]. Consistently, in this instance, the examiner used only that portion of the copending application disclosure that pertains to the claimed invention.

Further addressing *In re Vogel and Vogel*, the Court decided the correctness of the conclusion that a patent claim drawn to a process for packaging "pork" would be obvious over a pending claim drawn to a process for packaging "meat", since although "pork does not read on "meat", "meat" reads literally on "pork". However, the Court further noted "viewing the inventions in reverse order, i.e., as though the broader claims issued first, does not reveal that the narrower (pork) process is in any way unobvious over the broader (meat) invention disclosed and claimed in the instant application" *Id.* at 623. The examiner believes this is because, were the patent claim to broadly recite "meat", although "pork" does not read on "meat" (i.e., a species encompassed by the genus generally does not suffice to describe the genus), the specification states how the claimed process is to be carried out with "pork". The Court indicated that this portion of the specification, stating how the claimed process is to be carried out using pork, supports the patent claims *and may be considered*. *Id.* at 622.

In certain situations, the supporting disclosure may be used to define terms in a claim and to determine whether the invention claimed has been modified in an obvious or unobvious manner. See *Carman Industries, Inc. v. Wahl et al.*, 220 USPQ 481 (CA FC 1983). If modified in an unobvious manner,

there is no double patenting issue. In this instance, there can be no mistake that the invention claimed in the instant application is an obvious "variant" of the invention claimed in the patent, because the supporting disclosure of the latter teaches that the antigen-binding domains may be humanized.

If the instant claims were drawn instead to an unobvious "variant", or to an invention that might only be gleaned from consideration of portions of the disclosure that do not support the copending claims, such that the consideration would be improper, then there would be no double patenting issue. Because only those portions of the disclosure that support the copending claims has been considered, and those portions include a description of the "variant" claimed in the instant application, then, double patenting rejection is believed warranted.

Accordingly, the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the patent anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the patent

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

26. Claims 1, 4, 7-10, 13-15, 23, 24 and 31 are directed to an invention not patentably distinct from claims 12, 25 and 26 of commonly assigned application 10/554,851. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the above provisional rejection of the claims on the ground of nonstatutory obviousness-type double patenting.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending application 10/554,851, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies

as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

27. Claims 1, 4, 7-10, 13-15, 23, 24 and 31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 9, 13, 15-20, 33-35 and 41 of copending Application No. 10/572,740. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

The instant claims have been described supra.

Claims 1-7, 9, 13, 15-20, 33-35 and 41 of copending Application No. 10/572,740 are drawn to single chain bispecific binding molecules that bind human CD3 and EpCAM, wherein the domain that binds CD3 comprises the amino acid sequences of SEQ ID NO:98, 100 and 104 which share two consecutive amino acids with the instantly recited SEQ ID NO:10, compositions thereof and kits thereof.

Accordingly, the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the patent anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the patent

This is a provisional obviousness-type double patenting rejection because

the conflicting claims have not in fact been patented.

28. Claims 1, 4, 7-10, 13-15, 23, 24 and 31 are directed to an invention not patentably distinct from claims 1-7, 9, 13, 15-20, 33-35 and 41 of commonly assigned application 10/572,740. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the above provisional rejection of the claims on the ground of nonstatutory obviousness-type double patenting.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending application 10/572,740, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

29. Claims 1, 4, 7-9, 13-15, 23, 24 and 31 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 8 of US Patent 7,635,472. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

The instant claims have been described supra.

Claims 1-6 and 8 of US Patent 7,635,472 are drawn to single chain bispecific binding molecules that bind human CD3 and a cell surface antigen, wherein the domain that binds CD3 comprises the amino acid sequences of SEQ ID NO:55, 56 and 57 which share two consecutive amino acids with the instantly recited SEQ ID NO:10, compositions thereof and kits thereof.

While the claims do not further set forth that the antigen-binding domains may be humanized, it is noted that the specification of '472 discloses that the CDRs may be grafted into human antibody frameworks, i.e., humanized (see e.g., column 2).

Notably, MPEP § 804.II.B.1 states that when considering obviousness-type double patenting issues, the disclosure of the patent [or copending application] cannot be used as prior art, but "[t]his does not mean one is precluded from all use of the patent disclosure". MPEP § 804.II.B.1 continues, "[t]he specification can always be used as a dictionary to learn the meaning of a term in the patent [or application] claim". Citing *In re Vogel and Vogel*, 164 USPQ 619 (CCPA 1970), MPEP § 804.II.B.1 states, "one must first 'determine how much of the patent [or application] disclosure pertains to the invention claimed in the patent [or application]' because only '[t]his portion of the specification supports the patent claims and may be considered' " and " 'this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, **since only the disclosure of the invention claimed in the patent may be examined**" [emphasis added]. Consistently, in this instance, the examiner used only that portion of the copending application disclosure that pertains to the claimed invention.

Further addressing *In re Vogel and Vogel*, the Court decided the correctness of the conclusion that a patent claim drawn to a process for packaging "pork" would be obvious over a pending claim drawn to a process for packaging "meat", since although "pork does not read on "meat", "meat" reads

literally on "pork". However, the Court further noted "viewing the inventions in reverse order, i.e., as though the broader claims issued first, does not reveal that the narrower (pork) process is in any way unobvious over the broader (meat) invention disclosed and claimed in the instant application" *Id.* at 623. The examiner believes this is because, were the patent claim to broadly recite "meat", although "pork" does not read on "meat" (i.e., a species encompassed by the genus generally does not suffice to describe the genus), the specification states how the claimed process is to be carried out with "pork". The Court indicated that this portion of the specification, stating how the claimed process is to be carried out using pork, supports the patent claims *and may be considered*. *Id.* at 622.

In certain situations, the supporting disclosure may be used to define terms in a claim and to determine whether the invention claimed has been modified in an obvious or unobvious manner. See *Carman Industries, Inc. v. Wahl et al.*, 220 USPQ 481 (CA FC 1983). If modified in an unobvious manner, there is no double patenting issue. In this instance, there can be no mistake that the invention claimed in the instant application is an obvious "variant" of the invention claimed in the patent, because the supporting disclosure of the latter teaches that the antigen-binding domains may be humanized.

If the instant claims were drawn instead to an unobvious "variant", or to an invention that might only be gleaned from consideration of portions of the disclosure that do not support the copending claims, such that the consideration would be improper, then there would be no double patenting issue. Because only those portions of the disclosure that support the copending claims has been considered, and those portions include a description of the "variant" claimed in the instant application, then, double patenting rejection is believed warranted.

Accordingly, the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the patent anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the patent

30. Claims 1, 4, 7-9, 13-15, 23, 24 and 31 are directed to an invention not patentably distinct from claims 1-6 and 8 of commonly assigned US Patent 7,635,472. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the above provisional rejection of the claims on the ground of nonstatutory obviousness-type double patenting.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent 7,635,472, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Conclusion

31. No claims are allowed.

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571)

272-9935. The examiner can normally be reached on Monday through Thursday, 6:15AM to 4:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839 The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
January 28, 2011